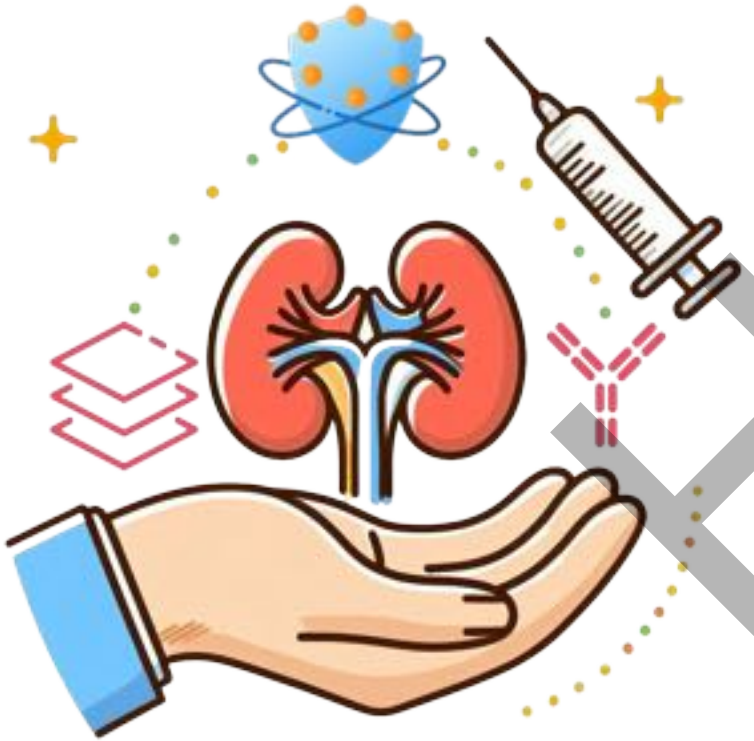
Complement in Renal Fibrosis and Repair

Friend or Foe



Prof.
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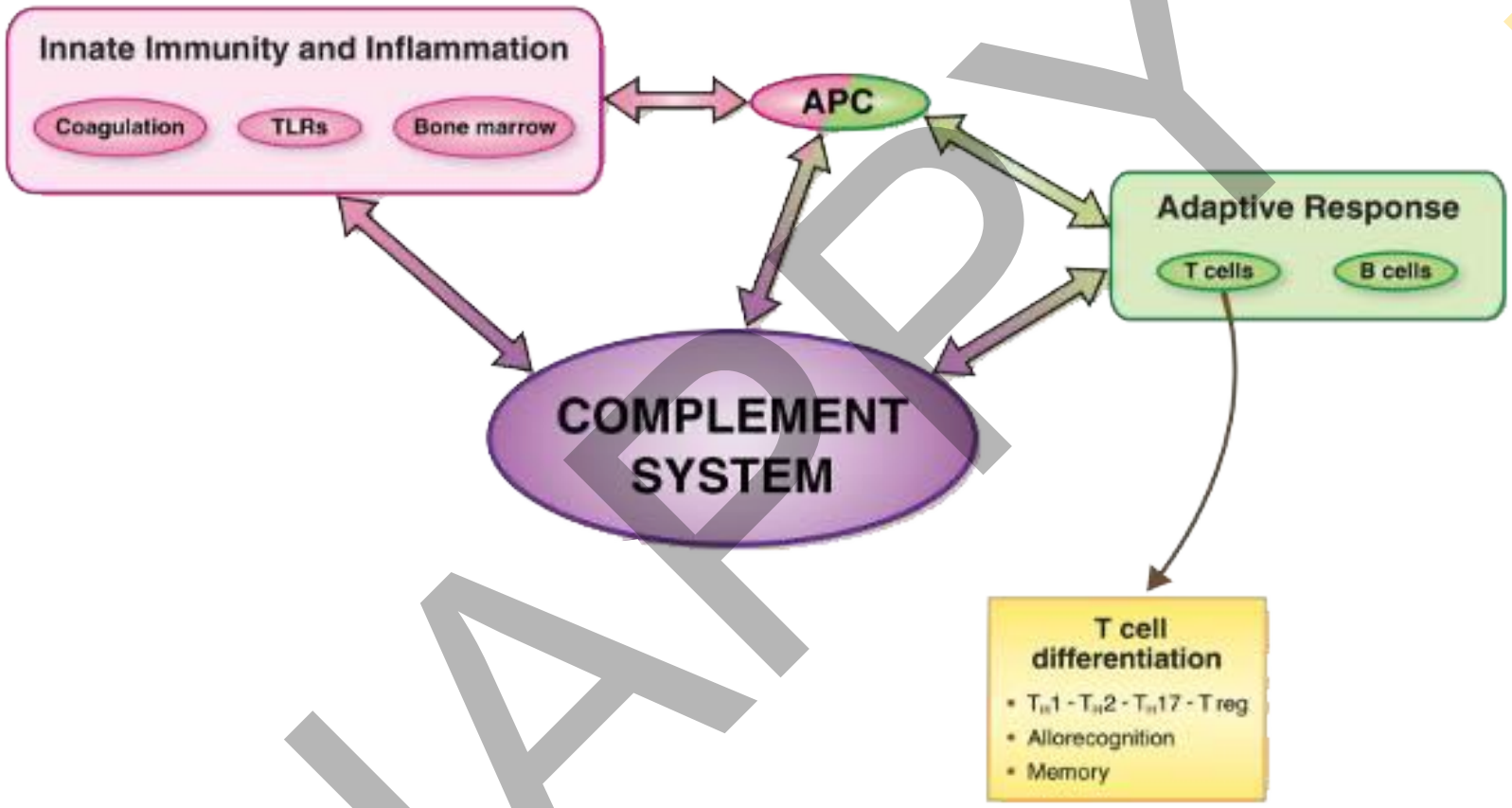


Fibrogenesis Tissue Repair. 2014;7:16.

AGENDA

- Complosome (sources and functions)
- Complement in ischemia reperfusion injury (IRI)
- Complement and renal fibrosis
- Complement in renal repair

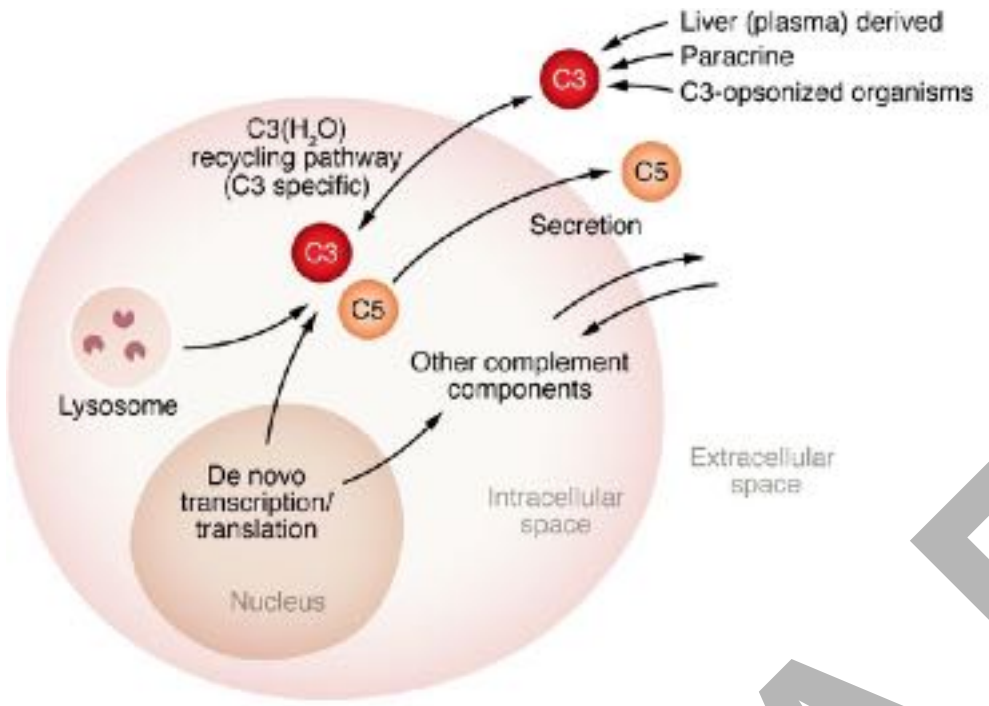
Complosome

High order protein complex (complement system) that is active intracellularly [Intracellular complement]

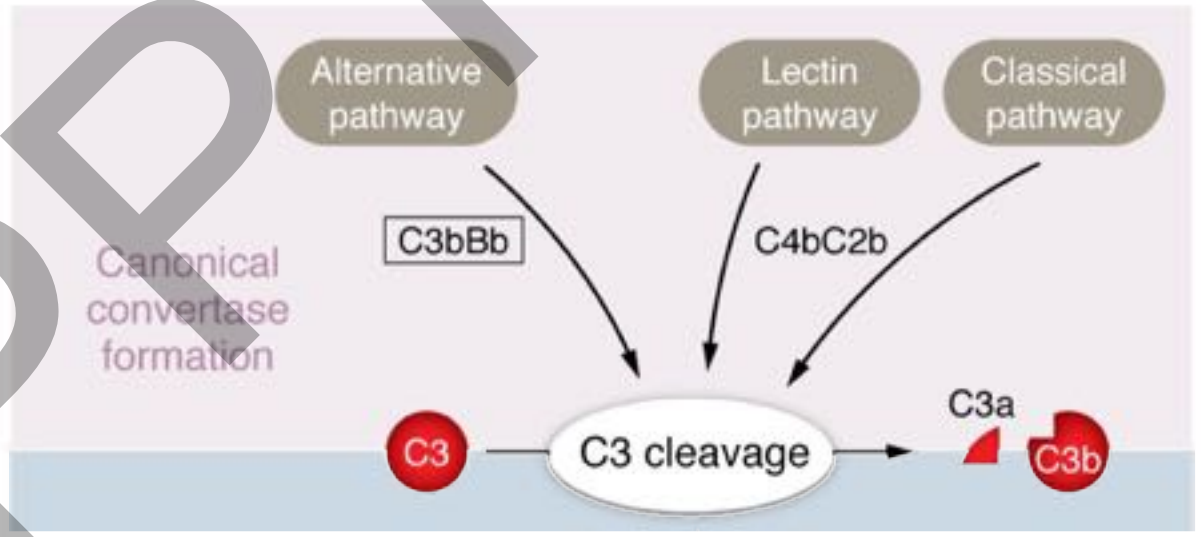
	Extracellular complement	Complosome
Encoding genes	Similar	Similar
Location	Plasma, interstitium	Within cell compartments
Activation	Classical / lectin / alternative	Intracellular proteolysis
Interaction	With each other	+ I.C. sensor/ effector system
Main function	Immune	Cell metabolism – autophagy - gene expression

Nat Rev Nephrol. 2023;19(7):426-439

Sources of complosome components



Canonical & non-canonical activation pathways of C3



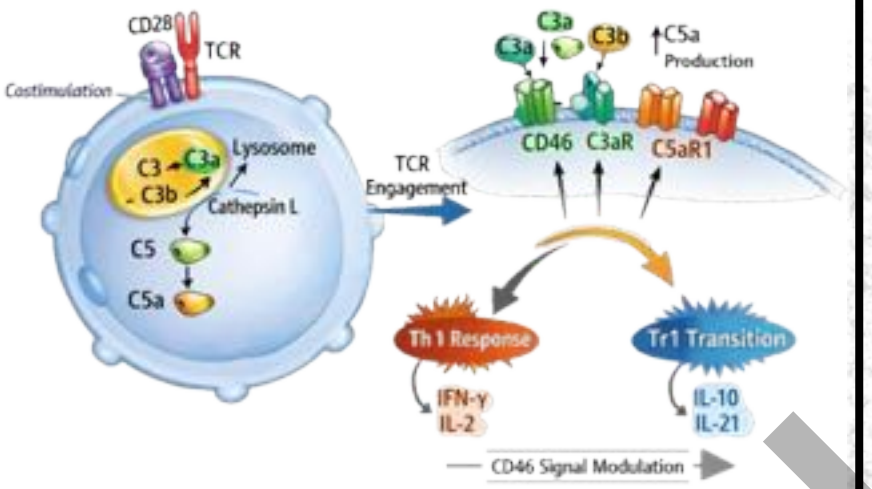
1. De novo synthesis
2. Uptake from plasma
3. Cointernalization w opsonized pathogens
4. I.C. stores from subcellular organelles

J Clin Invest. 2025;135(12):e188350

Key Triggers

01

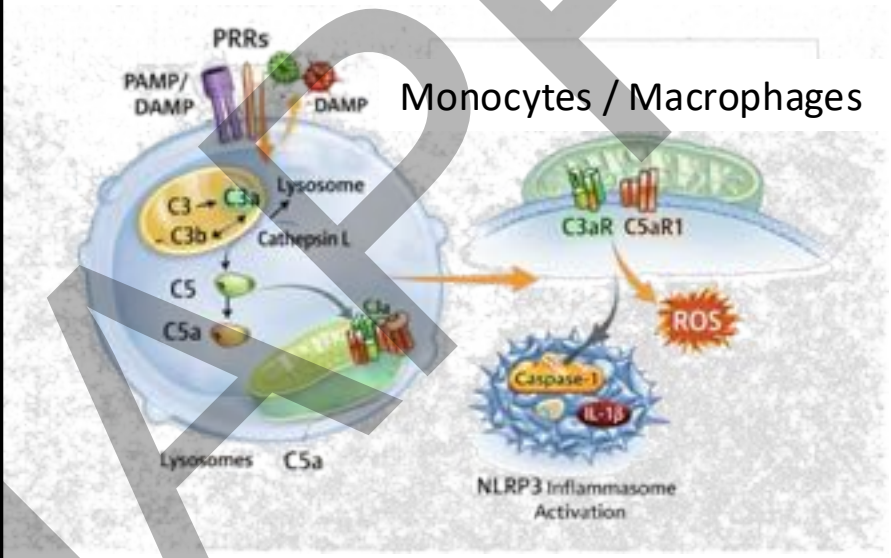
TCR and costimulatory signals in T cells



Immunity. 2016;45(2):240–254

02

Pattern recognition & danger signaling in innate cells



Eur j Immunol. 2023;53(12): e2250042

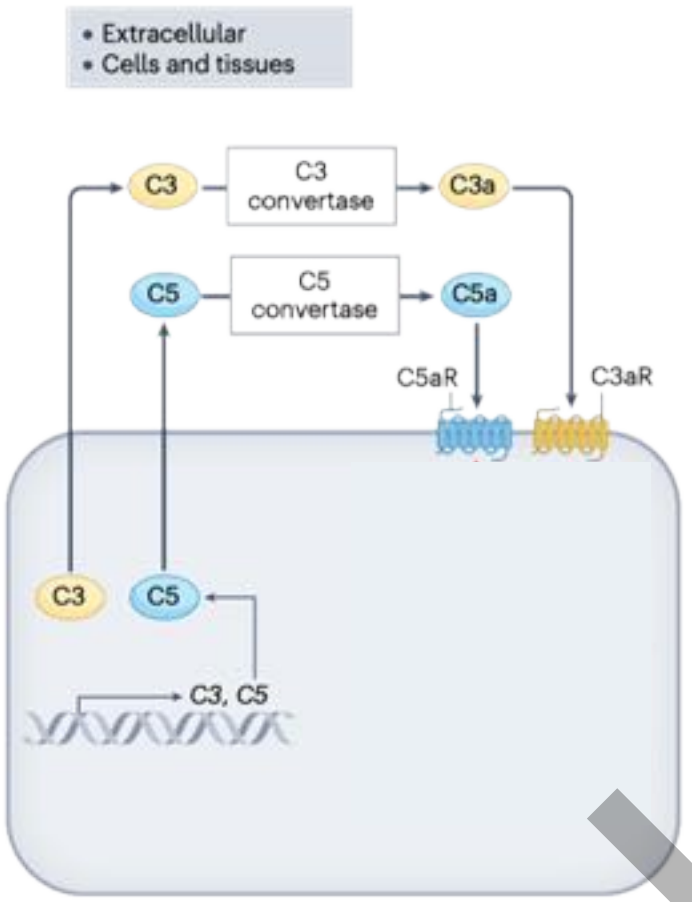
03

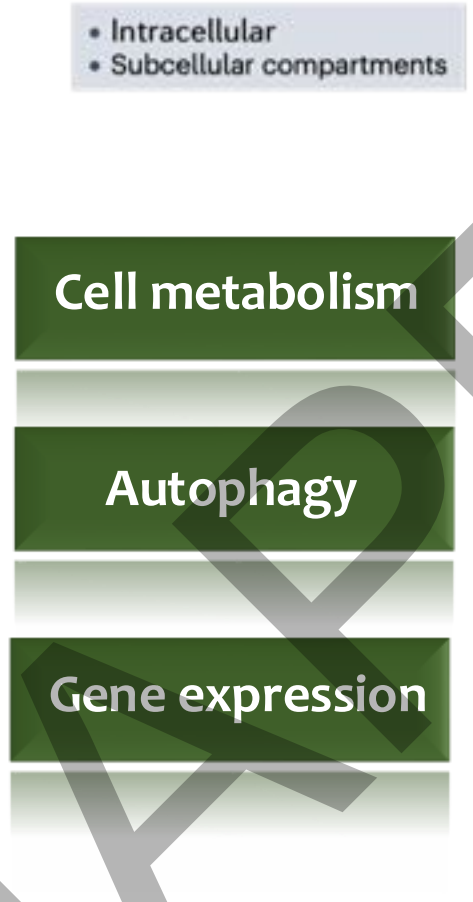
Non-immune cells

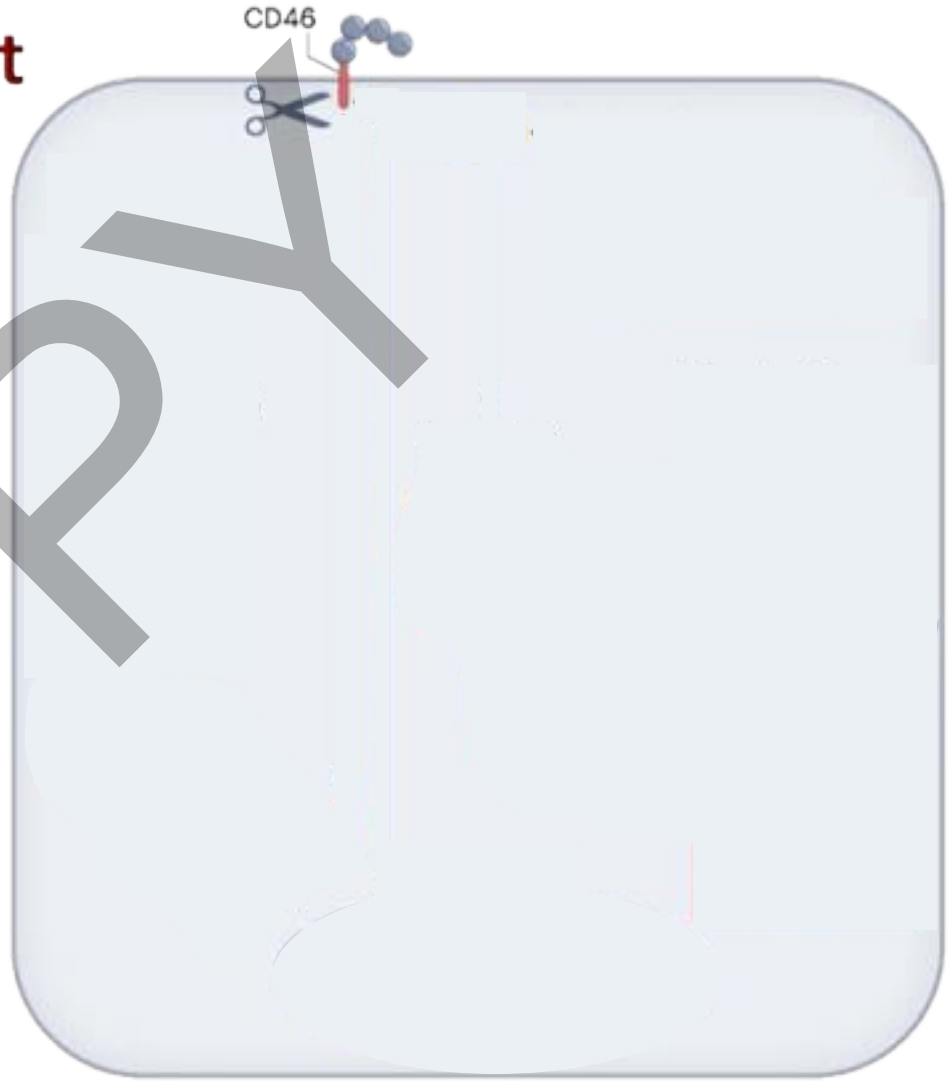
1. **Proinflammatory cytokines.**
2. **Hypoxic/metabolic stress.**

JCI Insight. 2025; 10(6): e184181

Non-immune functions of complement





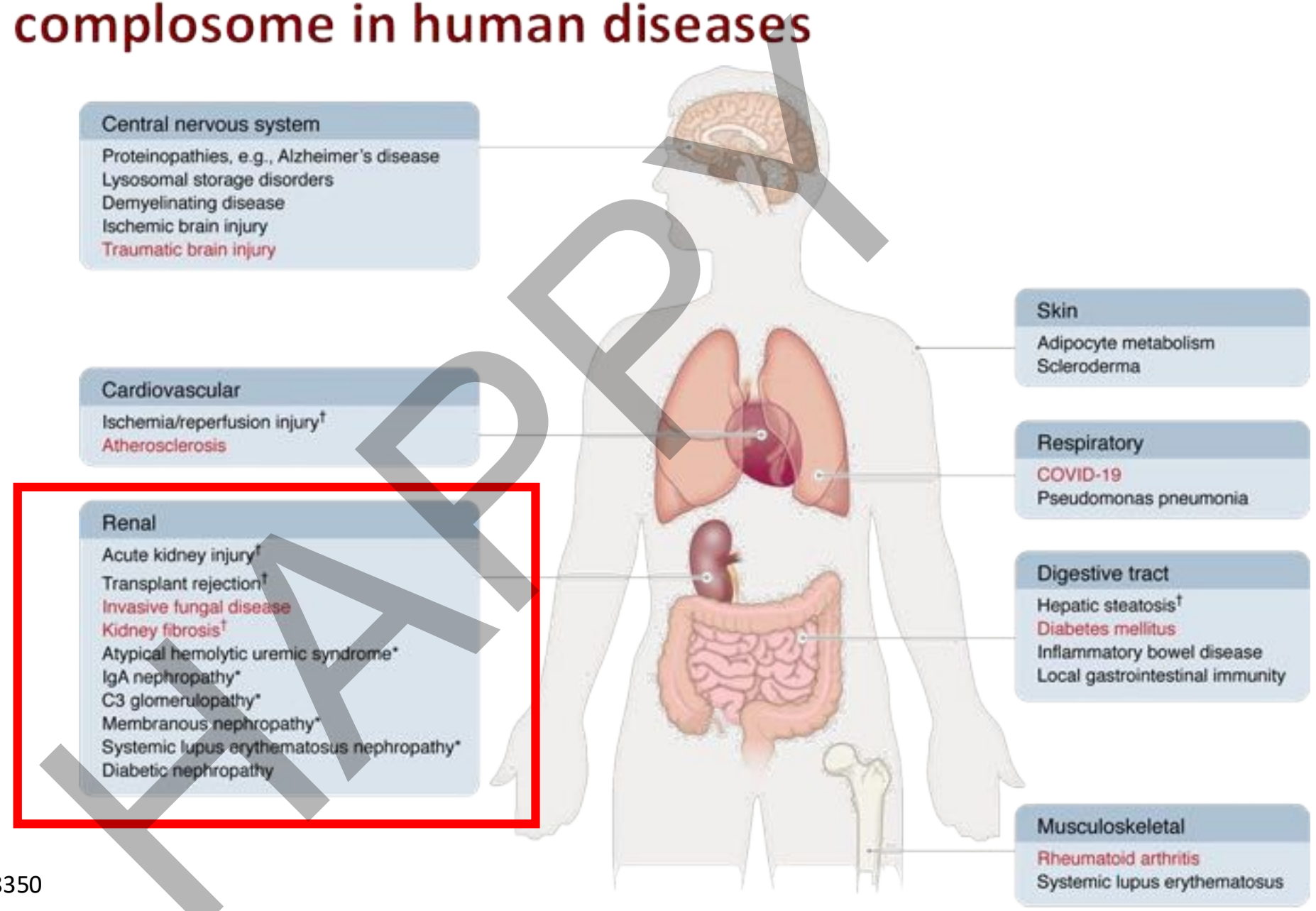


Induction of cell activation and function in an autocrine and/or paracrine fashion

- Maintenance of cell survival and homeostasis
- Control of basic cell physiological processes

Nat Rev Nephrol. 2023;19(7):426-439

Overview of the complosome in human diseases



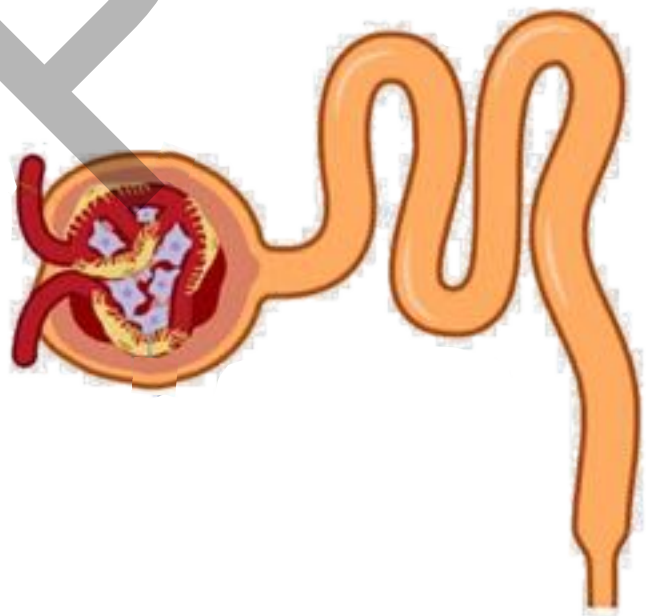
J Clin Invest. 2025;135(12):e188350

Main complement production sites in the nephron

All cells produce C1q and C3

C3a & C5a R in podocytes & mesangial C

All cells produce at least 2 regulators



Clin Kidney J. 2025;18(5):sfaf135

IRI

A common mechanism of injury in a wide variety of conditions ch.ch. by limited tissue perfusion

During ischemic period

Tissues are deprived of O2 & nutrients required for metabolism & homeostasis

Upon perfusion restoration

Endogenous ligands from damaged cells activate innate immune cells & exacerbate inflammatory tissue & organ injury

Fibrogenesis Tissue Repair. 2014;7:16.

Cellular response of PTCs to injury

J Clin Invest. 2025;135(12):e188350

Fibrogenesis Tissue Repair. 2014;7:16.

Adaptive repair

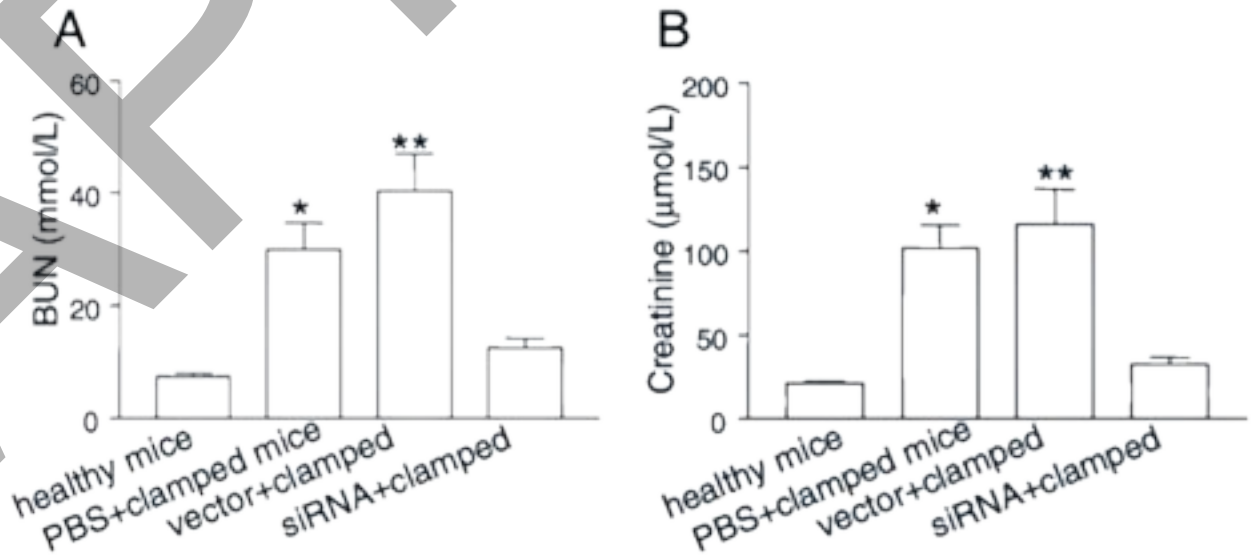
- Clear necrotic/apoptotic debris
- Maintain basic immune surveillance

Failed repair

- Persistent injury program
- Progression to renal fibrosis

Complement system following renal injury

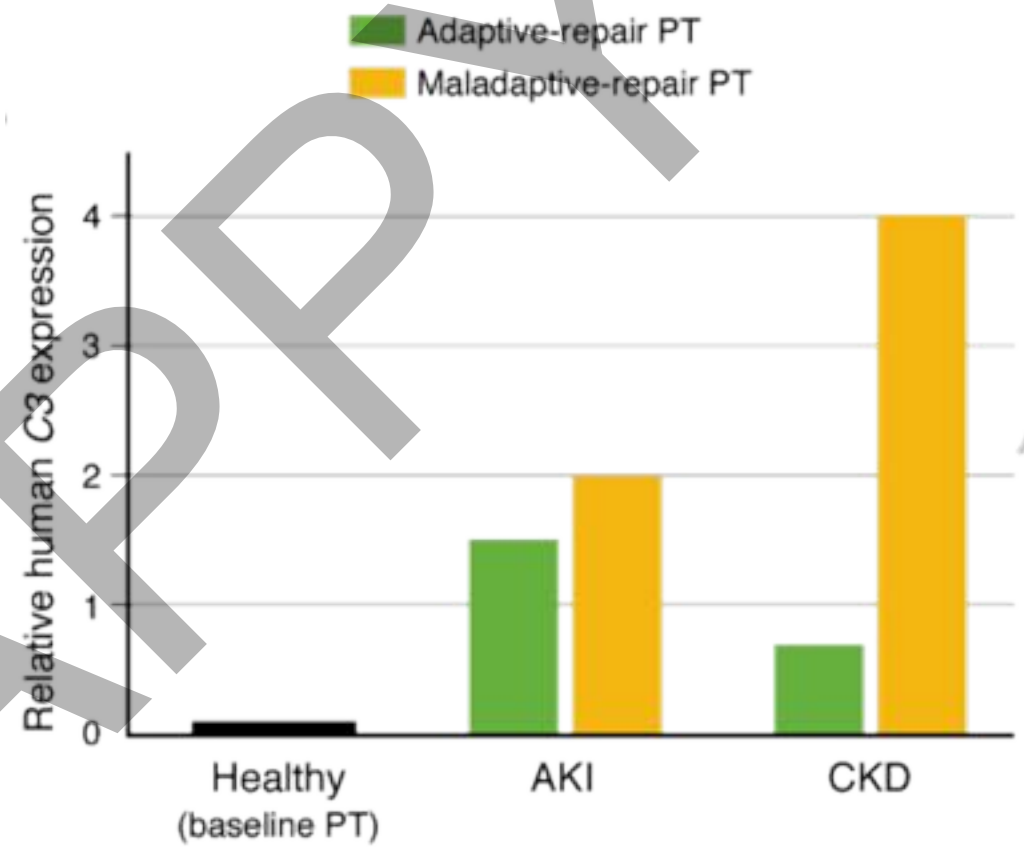
Preventing IRI in experimental mice using C3-siRNA



American Journal of Transplantation 2006; 6: 2099–2108

C3 gene activity in adaptive & maladaptive repair

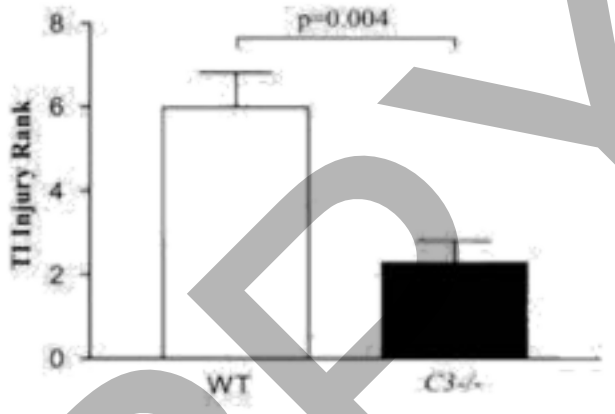
PTCs from healthy kidneys exhibit minimal C3 activity, whereas C3 expression is substantially elevated in maladaptive repair PTs across both AKI and CKD settings (*KPMP datasets analysis*)

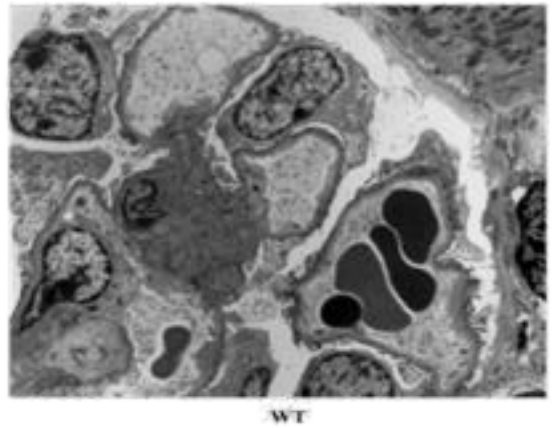


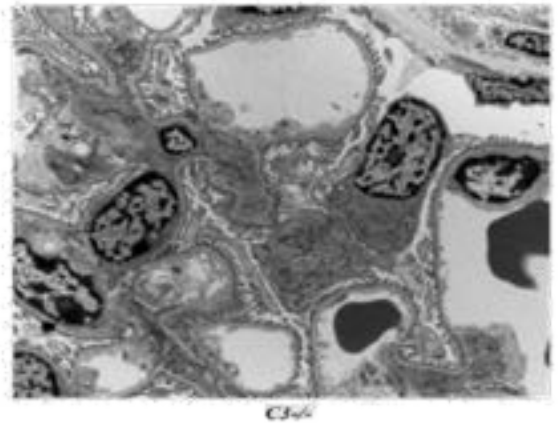
J Clin Invest. 2025;135(12):e188350

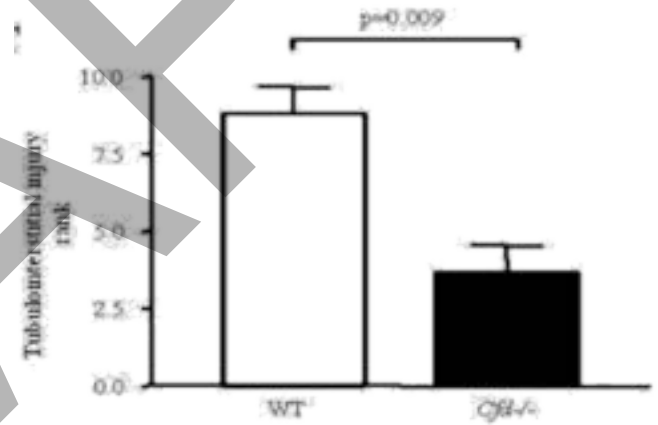
Complement and glomerulosclerosis

Mice deficient in C3 or Cf*d* and treated with adriamycin (FSGS model) show reduced fibrosis when compared with wild-type mice.





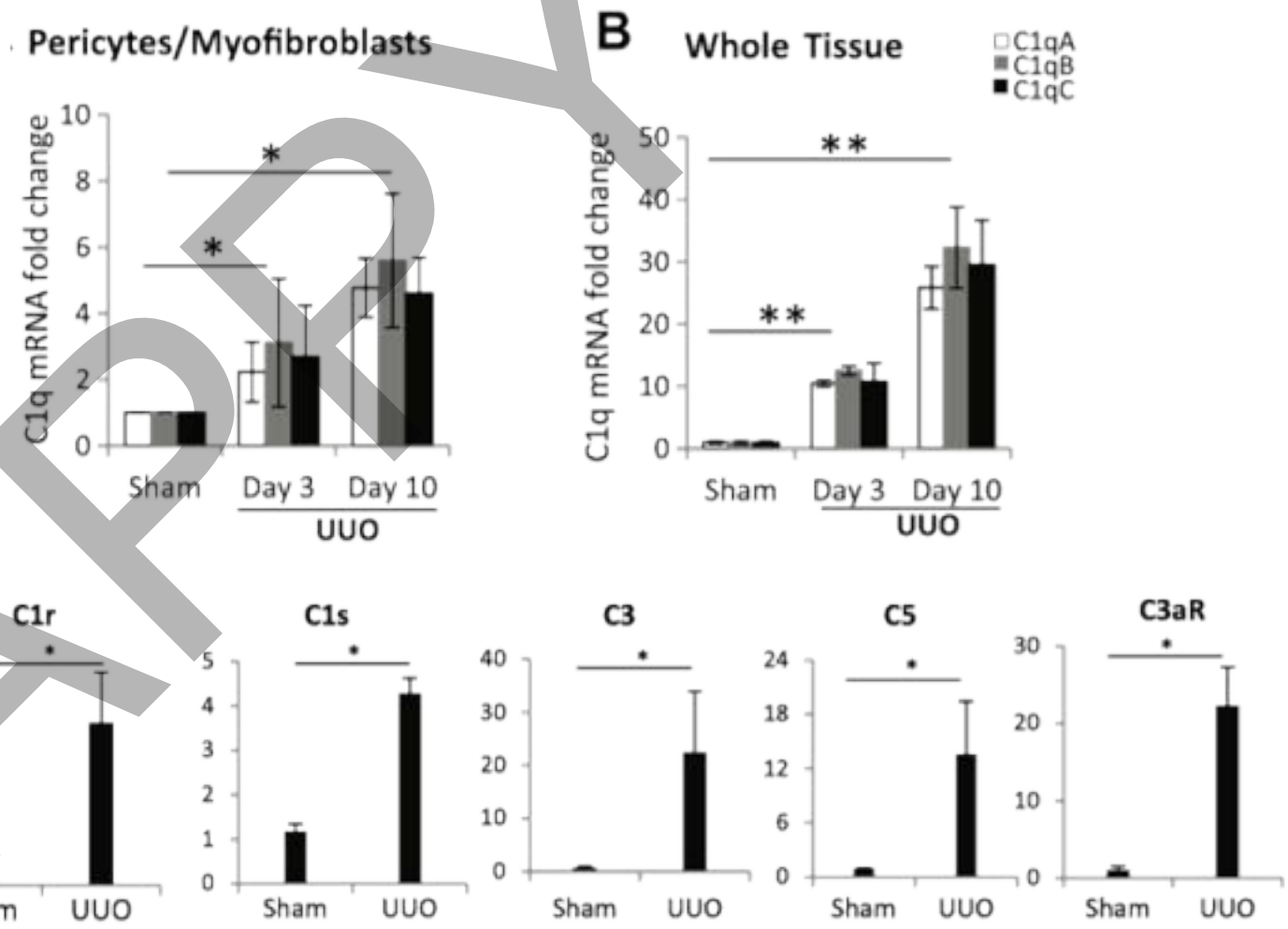




J Immunol. 2006;177(6):4094-102

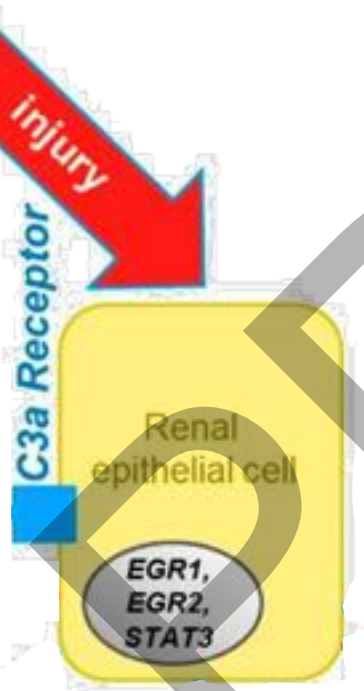
Complement and tubulointerstitial fibrosis

Upregulated expression of C1q, C3 fragments, C5, and complement receptors C3aR and C5aR, along with the presence of tubulointerstitial fibrosis using mouse models of CKD



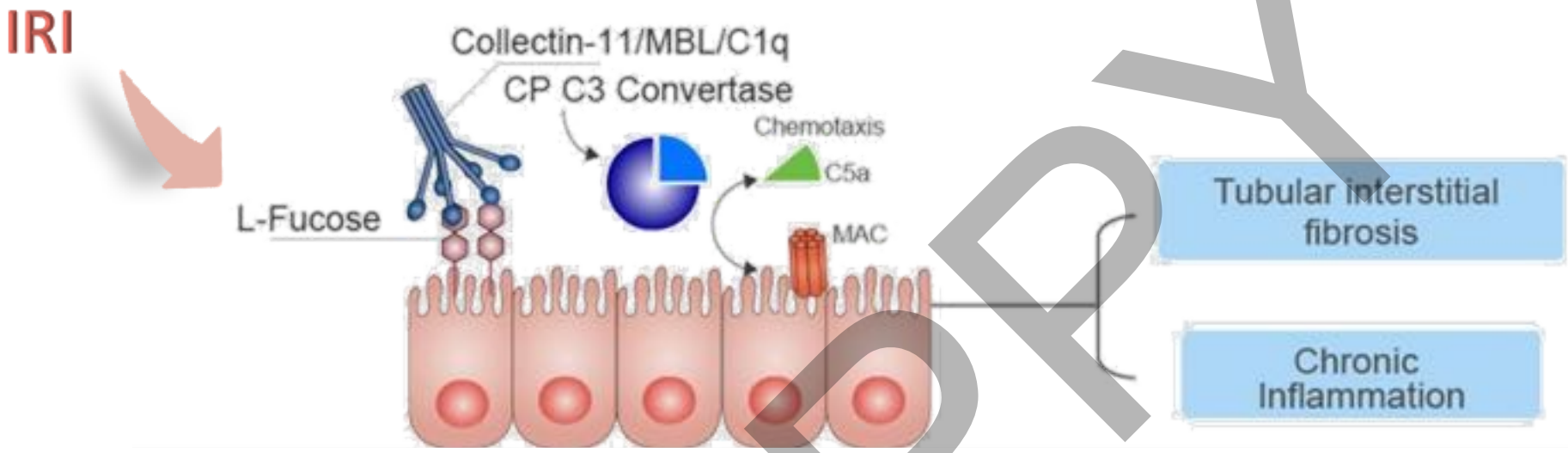
Am J Physiol Renal Physiol. 2017;312(3):F516-F532

Role of locally produced C3 in renal fibrosis



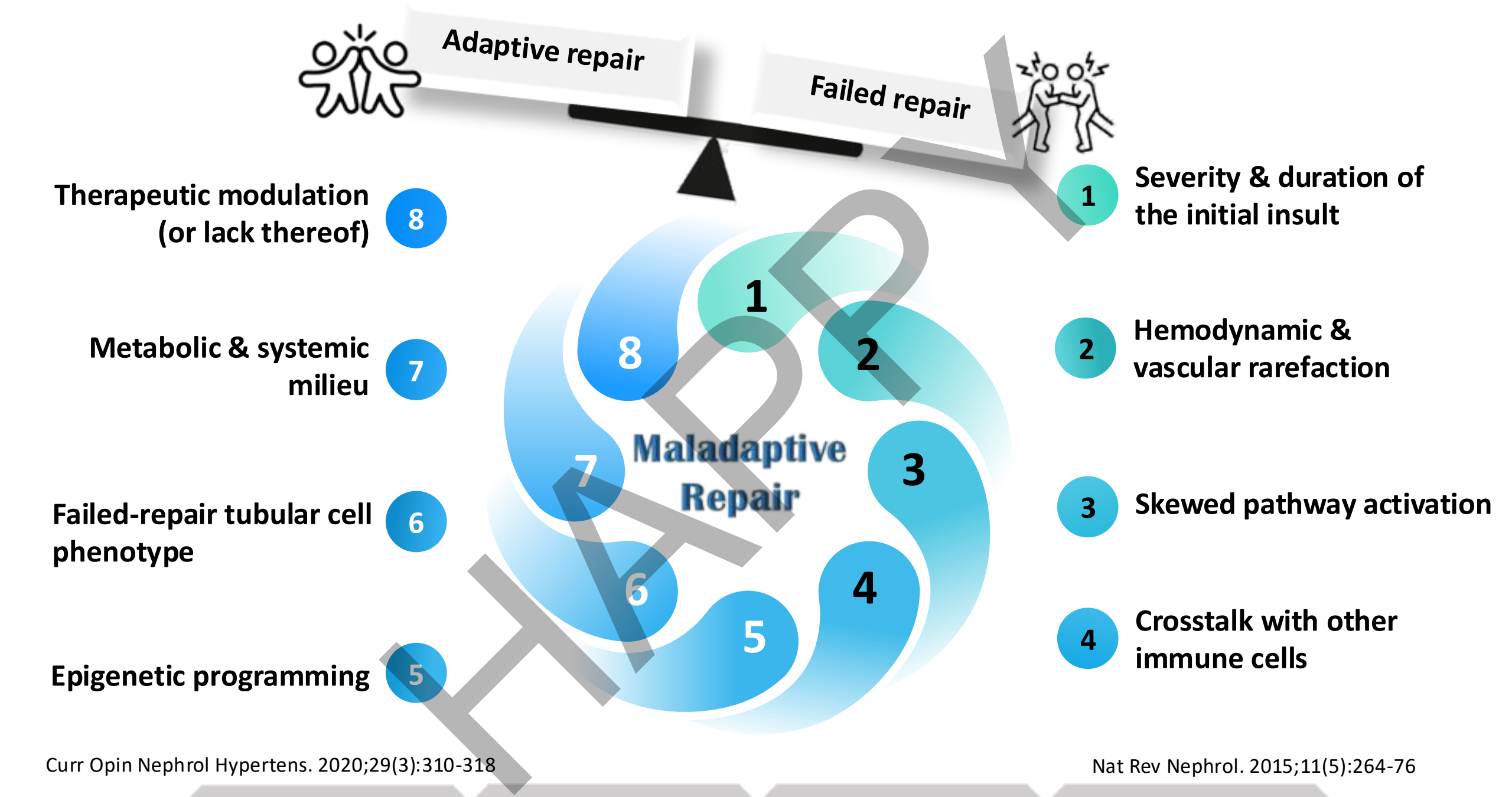
Int. J. Mol. Sci. 2024, 25, 12551

Role of lectin pathway in renal fibrosis



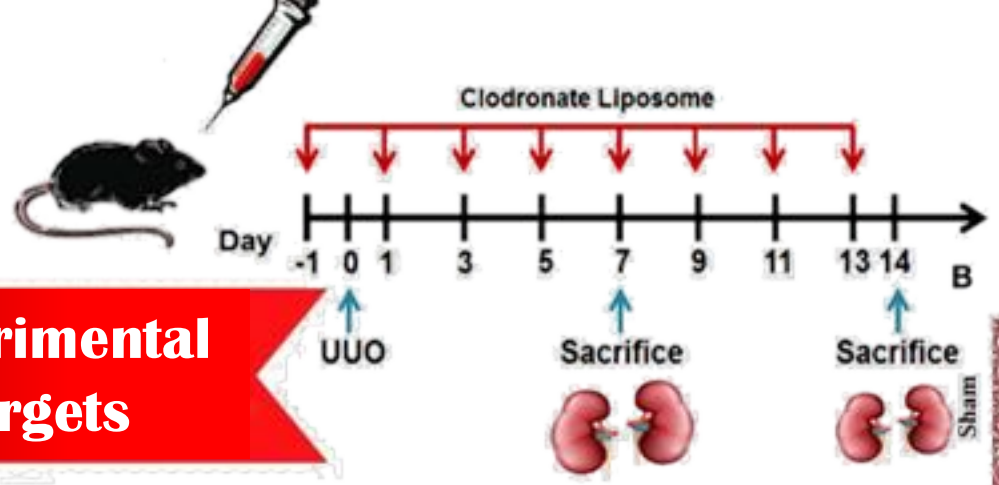
RTE expressed fucosylated glucose patterns upon IRI, which can be recognized by the lectin pathway pattern recognition receptor (PRR)

Front Immunol. 2020;11:734



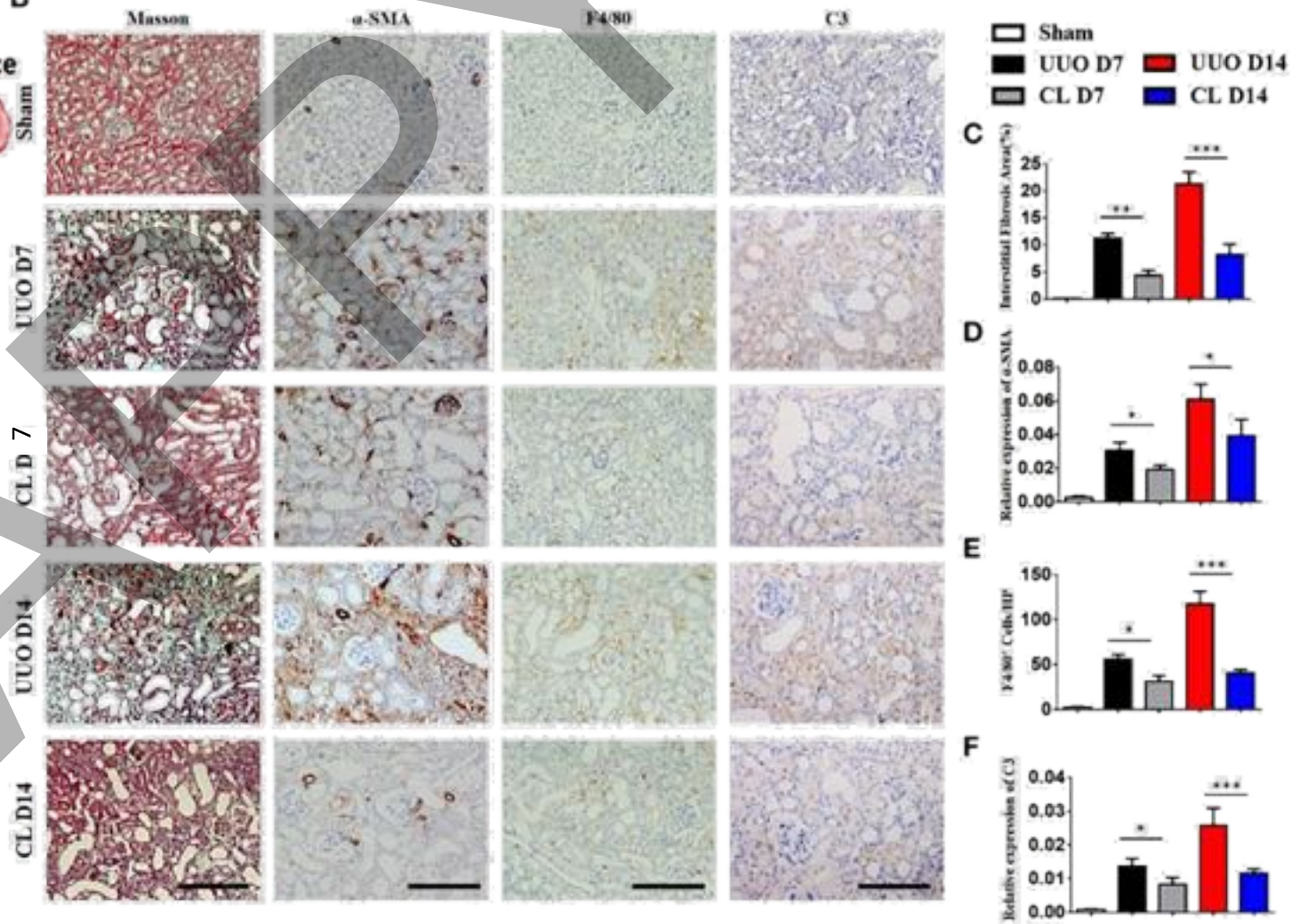
Curr Opin Nephrol Hypertens. 2020;29(3):310-318

Nat Rev Nephrol. 2015;11(5):264-76



Experimental targets

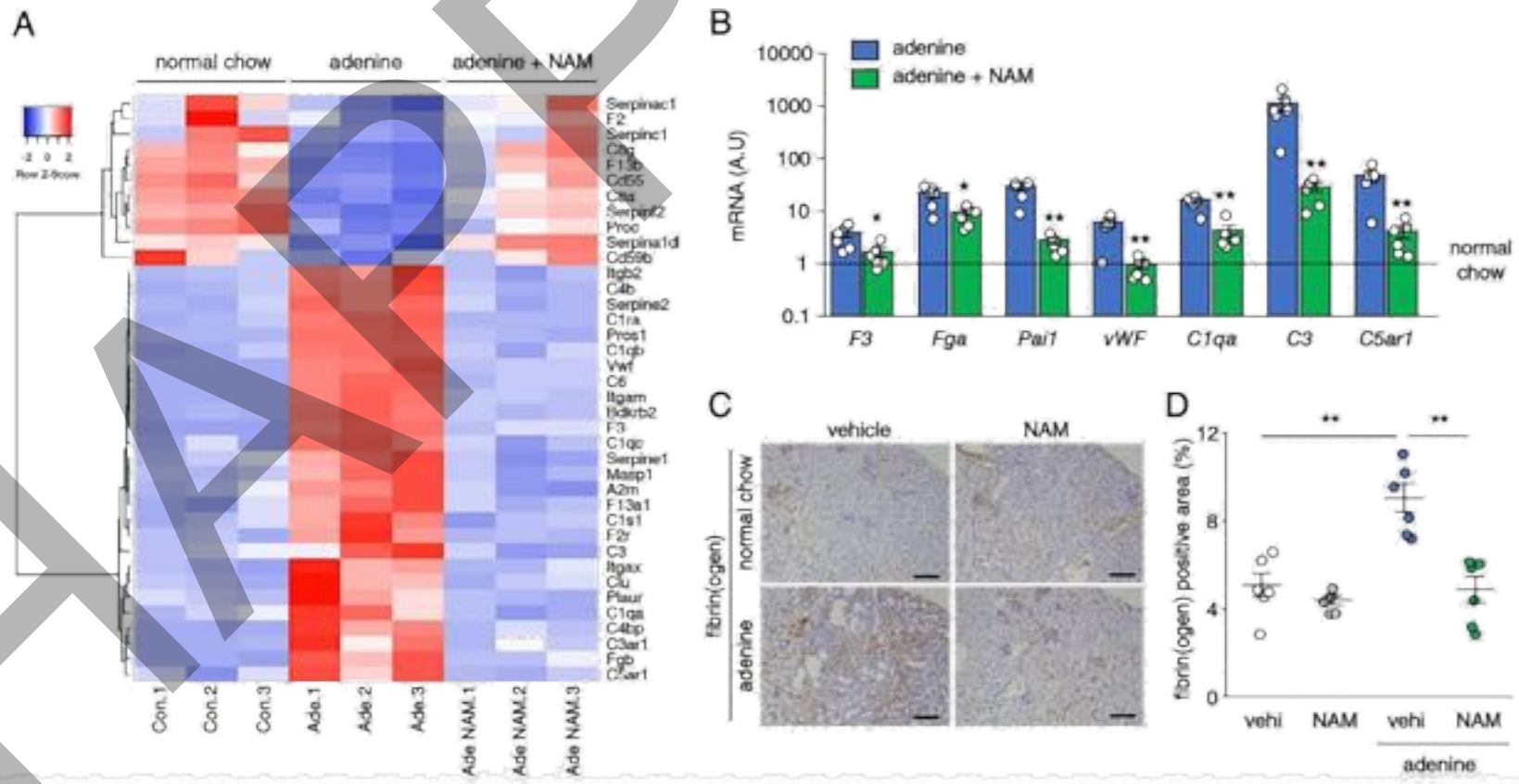
Macrophage depletion (*Macrophage-derived C3 and C3a*) protects against renal fibrosis by inhibiting C3 expression.



Front Immunol. 2018;9:2385

Experimental targets

Nicotinamide modulated the complement and coagulation cascades in adenine-induced nephropathy



FASEB J. 2025;39(23):e71263

Conceptual framework

In diseases where complement is a primary upstream driver (e.g., C3G, aHUS), early pathway-specific inhibition may indirectly limit fibrosis by rapidly extinguishing inflammation and endothelial/tubular injury

In more generic CKD (proteinuric, obstructive), complement appears as an amplifier of tissue injury and fibroblast activation; here, adjunctive targeting of C3aR/C5aR1 or the lectin/alternative pathways, is a rational anti-fibrotic strategy.

- The complosome contributes to cellular metabolism, autophagy, and regulation of gene expression.
- Following IRI, the complement system exhibits a balance between adaptive and maladaptive repair responses
- Dysregulated complement activation plays a pivotal role in maladaptive repair, leading to glomerulosclerosis and interstitial fibrosis.